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REVIEW ARTICLE

INTERVENTIONS TO IMPROVE ADHERENCE TO ANTIRETROVIRAL MEDICATIONS

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ABSTRACT

Background: Antiretroviral therapy has led to a substantial reduction in HIV associated morbidity and mortality. Efficacy of antiretroviral treatment in HIV/AIDS is showing inhibition of viral replication and reduction of viral load to a point where viral particles are undetectable in the blood of infected individuals. Increasing recognition of medication adherence is a crucial factor in treatment outcomes. This has led to the realization that HIV/AIDS is a chronic illness and hence the quality of life of PLWHA needs to be enhanced. The maintenance of viral suppression requires maximum adherence (at least 95%) to ART.

Objective: The objective of this review was to assess the recent literatures regarding interventions to improve antiretroviral medication adherence; to know factors affecting adherence, strategies to measure adherence to ART by reviewing research works done recently (2008-2013) on intervention to improve ARV adherence (adherence improving tools and strategies).

Method: This literature review was obtained from electronic search on pubmed, AIDS LINES, MEDILINE, PyschInfo and also search was conducted on individual journals and manuals.

Conclusion: Adherence to ART is closely tied to virologic, immunologic, and clinical outcomes. Improving adherence requires collaborating with the patient in an effort to understand and ameliorate individual impediments to adherence, generally by establishing dedicated time with every patient to educate, plan for adherence, and maintain support and collaboration throughout the course of treatment.

Keywords: Antiretroviral therapy, recognition of medication adherence, interventions to improve antiretroviral medication adherence

1. INTRODUCTION

1.1 HIV Infection and AIDS Worldwide

Human Immunodeficiency Virus (HIV) disease is a chronic infectious disease caused by the HIV, which is characterized by spectrum starting from primary infection, with or without the acute syndrome, followed by relatively long period of asymptomatic stage after which in most patient's progress to advanced and life threatening disease Acquired Immune Deficiency Syndrome (AIDS).[1]

HIV/AIDS is a global pandemic, with cases reported from virtually every country. At the end of 2011, an estimated 35.9 million individuals were living with HIV infection according to the Joint United Nations Programmed on HIV/AIDS (UNAIDS). More than 95% of people living with HIV/AIDS (PLWHA) reside in low and middle income countries; 50% are female, and 2.5 million are children <15 years.[2] In sub-Saharan Africa, there has been a dramatic increase in the number of HIV/AIDS patients, nearly two-thirds of PLWHA live in sub-Saharan Africa.[3]

Ethiopia is among the country most affected by the HIV epidemic with an estimated adult prevalence of 1.5 %, has large number of people living with HIV (approximately 800,000); and about 1 million AIDS orphans. [4]

The global distribution of the estimated number of PLWHA; i.e., the global prevalence has increased approximately fourfold since 1990, reflecting the combined effects of continued high rates of new HIV infections and the beneficial (life-prolonging) impact of antiretroviral therapy.[1]

1.2 Antiretroviral Therapy (ART)

ART is the administration of at least three different medications known as Anti-Retro Viral drugs (ARV) in order to suppress the replication of the HIV. Treatment with these combinations of drugs is also known as Highly Active Antiretroviral Therapy (HAART). ART is not a cure. It must be taken for life and is costly. ART changes a uniformly fatal disease to a manageable chronic illness. Successful use of ART suppresses HIV

viral replication, consequently slowing down disease progression, improving immunity and delaying mortality. Even if ART is not a cure, it prolongs and enhances the quality of life of PLWHA. Once ART is started, it has to be taken for life with better than 95% adherence.[4]

ART has shown to delay progression to AIDS, resulting in a greater and more sustained virologic and immunologic response and improve survival. In sub-Saharan Africa, there has been a dramatic increase in the number of HIV/AIDS patients on ART from just 100,000 persons in 2003 to 3.9 million in 2009 involving close to 40% of those in need of the treatment.[3]

Two sub-Saharan Africa countries, Botswana and Rwanda, have achieved universal access target (treatment coverage of 80% or more of patients in need) at the end of 2009 while countries such as Ethiopia, Zambia, Namibia, and Senegal are moving closer to the same target having covered 50–80% of patients in need of treatment .[5]

1.3 Anti Retroviral Drugs (ARV)

There are currently three major classes of ARV drugs: nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). [4]

NRTIs include the thymidine analogs stavudine and zidovudin; the deoxycytidine analogs emtricitabine and lamivudine; the deoxyguanosine analog abacavir sulfate; and the deoxyadenosine analogs of which didanosine is an inosine derivative and tenofovir disoproxil fumarate is a deoxyadenosine-monophosphate nucleotide analog (a nucleotide is a nucleoside with one or more phosphates). NNRTIs are a chemically heterogeneous group of agents that bind noncompetitively to reverse transcriptase adjacent to the catalytic site. Available NNRTIs include efavirenz, delavirdine, nevirapine and etravirine. PIs include amprenavir and its prodrug fosamprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. PIs competitively inhibit the cleavage of the gag-pol polyprotein, which is a crucial step in the viral maturation process, thereby resulting in the production of immature, noninfectious virions.[6]

Advance in retroviral medication result in precipitous declines in HIV associated morbidity and mortality. ARV medications have transformed HIV to a chronic condition requiring life-long treatment. The effects of ARV medications on prolonging life and preventing opportunistic infections have been well documented, and there is evidence that the resultant lower viral loads are associated with lower risks of HIV transmission to both unborn children and sexual partners.[5]

1.4 Adherence to ARV drugs

Adherence is the act or quality of sticking to something or to adhere to something. Adherence to medication is the degree of concurrence between client's behaviors (taking medication, sticking to diet, taking the right dose and at the right time) and following medical advice on medication regimen. The term 'medication adherence' in HIV/AIDS care specifically refers to the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function.[4]

It is act or quality of sticking to something, steady devotion, the act of adhering and best achieved through a collaborative process that facilitates acceptance and integration of medication regimen into an individual's daily life.[5]

Non adherence may mean not taking medication at all, taking reduced amounts, taking more medication than prescribed, not taking doses at prescribed frequencies or intervals or not matching medication to food requirements and self initiated holidays. Factors associated with non adherence include lower income, lower education, substance use, higher dose frequency and fewer adherence aids such as pillboxes and timers. The frequency and severity of side effects conflicts with daily routine, dietary recommendations, frequency of medication dosages, number o f medication dosages, psychological factors such as stress, anger, or denial and physical consideration such as fatigue and sleep.[7]

Adherence to HIV treatment is critical to the success of improving the quality of life and survival of people with HIV/AIDS. Interventions and services should be multifaceted, tailored for each patient, and delivered through a multidisciplinary team approach that includes the patient in collaborative treatment planning.[8]

The 2nd strategies predictors of progression on AIDS and death after CD4 count is adherence to therapy. A significant association exists between adherence and viral load suppression in which non adherence leads to the developments of antiretroviral resistant virus because full and durable viral suppression necessitates nearly perfect adherence stressing and promoting compliance will help to insure maximum benefit from HAART and reduce the development of resistance.[8]

Efficacy of ARV drugs in HIV/AIDS is showing inhibition of viral replication and reduction of viral load at a point where viral particle are undetectable in the blood of infected individuals. According to recent studies, ART regimens require 70–90% adherence in order to be effective. However, sustaining adherence to ART over the long term requires accurate and consistent monitoring, and this is a particular challenge for countries in sub-Saharan Africa. [5]

It is further challenged by various social and clinical obstacles where inadequate suppression of viral replication by ART are resulting due to poor adherence to therapy, low potency of the antiretroviral regimen, viral resistance to antiretroviral medications, and pharmacokinetic interactions causing inadequate drug delivery. The transmissibility of the antiretroviral resistant viruses from person to person further compounds the problem as a clinical and public health challenge.[5]

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1.5. Adherence Measurement Strategies

The measurement of medication adherence is a difficult both in clinical care and research settings. Quantifying the levels and types of medication adherence involved patient care has been the focus of many studies resulting in the identification of multiple direct and indirect measures. Given the significance of viewing medication initiation and continuation as a process involving stages of change, measurement tools have been developed to attempt 'matching' communication strategies to readiness for treatment. Some of the most recent work in the area of antiretroviral medication adherence measurement has supported the independent association of patient and provider reported adherence with multiple variables that influence adherence; accordingly areas to be explored more fully include incorporating a combination of patient and provider reporting and pharmacy refill data. A single isolated method of adherence assessment seems to be inadequate and impractical. Use of more than one ART adherence measures to capture more accurate information to determine adherence levels have been recommended. There may be no gold standard with which to measure adherence, there are several strategies available, each with its respective strengths and weaknesses.[9]

Clinical studies have employed medication event monitoring System (MEMS), pharmacy refill data, providers' estimates and directly observed therapy (DOT) or directly administered ART (DART) either alone or in combination to measure ART adherence. After being on ART for some time, the patient gets habituated to pill count exercise and manages to bring exact number of pills to the clinic. He/ she may either be throwing pills every day or removing them from the bottles just before visiting the clinic. It is obvious that being a patient enabled issue; any adherence measure related to patient (report/ pill count) has its own disadvantages owing to the psychosocial need of social desirability or merely to avoid reprimand from health care provider.[10]

1.5.1 Self-reports: Three main types of self-report adherence measures have been used include surveys, interviews and diaries. Each is relatively easy to use and inexpensive, although data from several studies suggest that self-reports tend to overestimate actual adherence. One study that explored adherence rates in hypertensive patients found that 67% overestimated their adherence when self-reports from diaries were compared with data from the Medication Event Monitoring System (MEMS) caps.[8, 9]

Among investigators studying HAART adherence, there is agreement that self-report surveys that ask about missed doses within a very short time frame, i.e. within one to four days, are more valid and reliable than surveys that ask the respondent to remember a week or more ago.[9]

1.5.2 Clinician Assessments: There appears to be few HIV-related studies that have assessed the accuracy of clinician assessments of actual or potential adherence of their patients. Preliminary data presented in abstract form suggest that physicians overestimate patient adherence to HIV medication.[10]

1.5.3 Pill Counts: One strategy to evaluate adherence is to view the actual pill container and calculate how many pills should be left, given the date of the inspection, dosing and last refill. Because pill counts often occur in provider offices, clients are able to manipulate the number of pills remaining prior to the visit. Unscheduled home visits to conduct pill counts have the potential to be more accurate. Regardless of where the count actually takes place, reported that weekly pill counts demonstrated marked intersubject and intrasubject variability, obscured by long-term averages.[8,10]

1.5.4 Prescription Refills: Prescription refills may be a mechanism for assessing adherence to antiretroviral medications. Theoretically, pharmacists could work closely with health care providers and patients, informing both parties when medications are not being filled as directed. Unfortunately, such a close working relationship rarely exists in practice and patients may fill their prescriptions at different pharmacies. Although prescription refills could be monitored by the payer, insurance status often changes and thus, the payer source. Gaining access to pharmacy records remains difficult and the relationship between refills and actual ingestion of medications is not always clear.[9]

1.5.5 Biological Assays: Blood or urine biological assays can be used to measure adherence to treatment. Two main types of assays are available, but their use in monitoring adherence is controversial. Marker assays are based on materials that can be added to a drug and are easily detected, typically in the urine. Direct assays refer to testing for the presence of the medication itself in the blood or urine. Given the half-life of most medications, direct and indirect assays have the capacity to only measure adherence for the most recent doses taken, and not over longer periods. Biological assays to measure levels of antiretroviral medications and their metabolites are not commercially available at this time, thus further limiting this as a viable strategy to monitor adherence. Studies assessing composite 'scores' derived from self-administered questionnaires and plasma levels of PI have supported the value of plasma PI levels as an objective marker of antiretroviral therapy.[8, 10]

1.5.6 Medication Event Monitoring System: MEMS bottle caps are thought by some to provide a valid and reliable measure of medication adherence. These devices are special bottle caps that contain computer chips that fit on standard medication containers. The microchip stores the date and time each time the medication container is opened and closed. A long-life battery that cannot be switched on or off is also included. Data are retrieved by downloading the information from the cap device to a computer, which provides a spreadsheet display of an overview of individual adherence.[9, 11]

1.5.7 Adherence to HIV Treatment Regimens: This strategy may not work well when a large number of pills and complex treatment regimens are prescribed. In a sample of hypertensive patients, compared pill counts and MEMS data and found that each method identified different patients as being non-compliant. Investigators

at the University of California at San Francisco note that MEMS data can be scored only as "opened/closed" as many patients take out their entire supply of pills for the day and place them in their pockets instead of carrying around the medication bottles.[9,11]

1.6. Factors Associated with Adherence and Non adherence

Adherence to ART can be influenced by characteristics of the patient, the regimen, the clinical setting, and the provider/patient relationship. To assure adherence, it is critical that the patient receive and understand information about HIV disease, the goal of therapy, and the specific regimen prescribed.[12]

1.6.1 Patient factors

Patient factors that have been studied include; sociodemographic factors –such as gender, ethnicity, age, employment, income, education and literacy: and psychosocial factors such as active drug and alcohol use, degree of social support, social stability, depression and other psychiatric illness. Sociodemographic factors do not seem to adherence behavior, although some studies have found that male sex, white ethnicity, older age higher income and higher education correlate with better adherence.[11,12,13]

On other hand numbers of psychosocial factors have been found to strongly influence adherence; depression, psychiatric illness and active alcohol or drug use prevent patients from adhering to treatment. Social support helps patients to adhere better. A patient knowledge of his/her medication regimen and a patients understanding of the relationship between non adherence and build up of resistance to medication also predict better adherence. A patient belief and confidence in therapy.[13]

1.6.2 Medication factors

HAART consist of complex regimen that include up 20 pills a day with multiple dosing throughout a day and specific food and fluid related instructions. These are often difficult to follow for patient and contribute poor adherence. The higher the pill burden the lower is the adherence. A patient who reported experiencing "severe" side-effects, including hallucinations and insomnia, which affected his/her ability to work, discontinued ART in the early stages of treatment.[14]

ARV medication often have side effect, some of which are temporary (diarrhea, nausea and vomiting) while others may permanent or longer lasting (peripheral neuropathy, physical change in body appearance, lipoatrophy, lipodystrophy and metabolic change). Studies have shown that when patients experience side effect they tend to stop treatment or take it irregularly. [12, 14]

1.6.3 Patient-provider's relationship

The patient–provider relationship play an important role in improving adherence to prescribed medication in chronic disease. It is believed to motivating factor for adherence to HAART. Trust and confidence in provider has been found to influence adherence positively. Communication barriers were thought to contribute to poor adherence. Providers felt that this primarily affected patients who spoke languages different from those of their providers.[14]

1.6.4 Disease characteristics

Prior opportunistic infections contribute to increased adherence. Patients who have had serious OI may perceive their illness to be severe and adhere better to their treatment. Feeling well after taking treatment was reported as both barriers to, and facilitators of adherence.[7]

1.6.5 Clinical setting/health system

Aspects of clinical setting may associated with improved adherence. Different determinants of adherence are depicted in Figure 1. A friendly and supportive and non judgmental attitude of health care providers, convenient appointment scheduling and confidentiality contributes to better adherence. Most patients interviewed felt that clinic waiting times were too long. This contributed to their dissatisfaction with clinic services and made them more likely to stop coming to the clinic to pick up their medications.[16] The major factors associated with adherence and non adherence are mentioned in Table 1.

Again, despite an association being intuitive, clinical studies addressing the relationship between the clinical setting and adherence behavior are very limited. Dissatisfaction with prior experience in the health care system has been associated with non adherence.[17]

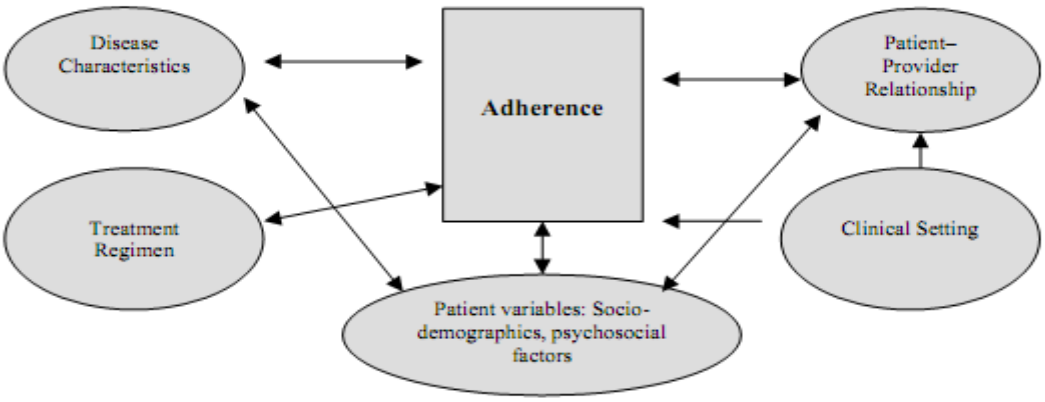

Figure 1: Determinants of adherence[15]

Table 1: Factors associated with adherence and non adherence[14].

Demographic Factors Individual patient attributes	Associated with adherence: Being in school Inconsistent or no association with adherence or nonadherence: Age, sex, race
Socioeconomic status	ssociated with nonadherence: Housing instability
Substance use and coping skills	Associated with adherence: Less alcohol use, less recent drug use (past 3 months) Associated with nonadherence: Depression-withdrawal coping style or self-destructive escape coping style, younger age of first marijuana use
Psychologic/ Developmental	Associated with adherence: Self-efficacy, higher life satisfaction on the quality-of-life scale, lower levels of psychologic distress, concrete rather than abstract reasoning skills, belief that medication would "most definitely" improve their quality of life. Associated with nonadherence: Depressive symptoms, symptoms of anxiety, sexual abuse under age 12 years, prior suicide attempt(s) Inconsistent or no association with adherence or nonadherence: Youthful feelings of "invulnerability"
Sexual risk	Associated with adherence: Less likely to have bartered sex during their lifetime, more likely to have used condoms with recent sex partners, less likely to have had a sexually transmitted disease since learning their serostatus
Disease Factors	Associated with adherence: Reduced viral load, CD4+ level ≥ 500 cells/μL Associated with nonadherence: Detectable viral load,later disease stage
Medication Factors	Associated with adherence: Fewer drugs prescribed, medication-related adverse effects (both physical and psychologic) Associated with nonadherence: Length of treatment with antiretroviral medications self-assessment of adherence by patient

2. SIGNIFICANCES OF THE LITERATURE REVIEW

As more people gain access to ART, new initiatives are n eeded to help ensure that patients adhere to treatment. The maintenance of viral suppression requires maximum adherence (at least 95%) to ART. Insufficient adherence to ARVs may result in treatment failure and the emergen ce of drug resistant strains of HIV and require a change to second-line treatment regimens, thereby greatly increasing treatment costs. This literature review helps to know factors affecting adherence, trategies to measure adherence to ART and research recently (2008-2013) done on intervention to improve ARV adherence (adherence improving tools and strategies).

3. OBJECTIVE OF THE REVIEW:

The objective of this review was to assess the latest literatures regarding interventions to improve antiretroviral medication adherence.

4. METHODS

This literature review was obtained from electronic search on pubmed, AIDS lines, MEDILINE, PyschInfo and also search conducted on individual journals and manuals. The search words or phrases were adherence, antiretroviral medication and intervention to improve adherence to antiretroviral medication. Each manuscript was analyzed according to all characteristics: purpose, conceptual framework, research question/hypothesis, variables, sample measures/instruments, method/statistical procedures, results, interpretation, recommendation and implication for health care. Qualitative and quantitative studies reporting original data on intervention to improve ARV medication adherence among HIV infected patients from 2008-2013 were included.

5. INTERVENTION TO IMPROVE ADHERENCE TO ARV DRUGS

Increasing recognition of medication adherence as a crucial factor in treatment outcomes has sparked a number of recent studies investigating methods to support and improve adherence. Continuous monitoring of both adherence and correlating it with clinical outcomes will create an interactive feedback mechanism that could lead to optimal clinical states and improved quality of life for patients. There are needs for further research and development in the area of ART adherence, adherence support, and patient behavior[14]

Diagnosing and treating health problems such as depression, reducing substance abuse, improving patient's and providers relationship, counseling and enhancing family, and community support mechanisms are shown to improve adherence, as well as intervening on modifiable barriers to adherence before starting ART. A meta-analysis by Amico and colleagues indicated that adherence interventions may be efficacious when targeted at individuals who are identified or anticipated to have poor adherence.[18]

The few investigations of interventions indicate that electronic reminders, pill organizers, MEMS to record dosing behavior, use of internet, educations services, use of phones, and so forth can also enhance adherence. However, most of these technologies have not had thorough scientific evaluation and their efficacy and cost effectiveness may not be as high as expectations. Cell

phone message reminders and web-based interventions require patient resources and literacy which could create obstacles to their applicability in developing country.[12]

A recent systematic review published by the Cochrane Database of Systematic Reviews reached similar conclusions. It cited diverse methodological problems and issues of study quality, among others as problems underlying the scant evidence on adherence improvement interventions and called for standardized and methodologically rigorous trials of interventions to improve and measure adherence to antiretroviral treatment.[16]

5.1. Adherence improving tools

5.1.1. Telephone reminders and calls

Telephone reminders are being tried out in some studies on adherence. There are several limitations to its uses: it is labour intensive for staff, patients must have telephone at all time and cost issue. With over 230 million cell phones in use and 7 billion text messages sent every month in the United States, text messaging or short message service (SMS) has become a common mode of communication among youth, including those who are economically disadvantaged. This low-cost, convenient technology has provided benefit in a variety of health care settings and has been shown to be an effective tool for behavior change. Mobile phones have been shown to improve chronic disease management in developed countries and have been proposed as a potential strategy to support ART adherence in developing countries.[15]

Reminder devices, however, have shown mixed results and few data are available for resource-limited settings. Encouragingly, a study conducted in Mombasa, Kenya, found that alarm devices significantly improved non-ART medication adherence rates among women attending sexually transmitted disease and family planning clinics.[19]

Evidence suggests that text messaging interventions may increase medication adherence among children and adolescents living with other chronic diseases such as asthma and diabetes (improve). Several studies have used both daily and weekly unidirectional, standardized SMS medication reminders for HIV-positive individuals in low-resource settings, but no published data have evaluated SMS medication reminders among youth living with HIV/AIDS in the United States. In particular, text messaging is well suited as a vehicle for ecological momentary interventions; that is, mobile technology can provide treatment to patients in real time and in their natural environments. Additionally, recent reviews of the literature on text messaging interventions for health behavior change have identified key characteristics for success; including interactivity and tailoring of messages, which were associated with higher retention rates in multiple studies.[16]

Pilot study conducted on youth in the Children's Hospital of Philadelphia on 25 youth enrolled over 6 month period 21 youth (84%) complete the study. The intervention was rated highly on indicators of satisfaction: at the 24-week follow-up, 17 of 21 (81%) participants who completed the study said they would like to continue to receive text messages after the end of the study, and 20 of 21 (95%) participants indicated that the text messages helped them "very much" to miss fewer doses of medication. During the study period 15,387 messages were sent and received through the Intelecare platform. Of the outgoing messages sent 1167 messages were not delivered and 14,220 messages were successfully sent. Of the 7110 messages requesting a response, 3414 (48.02%) text message replies were sent by participants indicating whether they took their medications.[20]

A randomized controlled trial of four SMS reminder intervention with 48weeks of follow up on 735 patients older than 18years participant' conducted in Kenya. They had been receiving weekly SMS reminder. These weekly reminders were also effective at reducing the frequency of treatment interruptions, which have been shown to be an important cause of treatment resistant failure in resource-limited setting. Like other successful adherence interventions, the intervention was effective in part by preventing the decline in adherence seen in the control group from 60 to 46% achieving 90% adherence over 48 weeks. Despite SMS outages, phone loss, and a rural population, these results suggest that simple SMS interventions could be an important strategy to sustaining optimal ART response. Preventing adherence-related treatment failure is especially important in resource-limited settings wherein second-line therapy is up to 17-fold more expensive than 1st line therapy and often unavailable. On this study adding words of encouragement in the longer text message reminders was not more effective than either a short reminder or no reminder.[21]

Although previous studies have shown benefit with individualized adherence tools, future cell phone based interventions should investigate how message form and content influences HIV and other chronic disease-related behavior. Message content must also take into account the common practice of shared mobile phone use and the potential that individuals will change phones numbers. It is also interesting to note that weekly reminders improved adherence, whereas daily reminders did not.[21]

Further research is needed to distinguish the mechanisms as to why the weekly messages were most efficacious. In a sub-study of a larger multicenter study 282 patients were studied with approximately 50% receiving 'usual' approach to medication adherence counseling and 50% receiving additional 'intensive' telephone counseling (16 calls over 96 wks). No increased level of adherence or virologic improvement was noted in those individuals receiving more intensive telephone counseling. It should be noted that other trials have demonstrated some increased efficacy with 'telephone' counseling as yet another component of overall care.[21]

Lima and colleagues conducted a study to examine the effect of a telephone consultation service (Warm line) on the clinical outcomes of HIV-infected patients who were prescribed antiretroviral salvage therapy regimens and had a viral load at least 1,000copies/ml at the baseline assessment. The study found that participants who received the Warm line consultation demonstrated

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significant declines in viral load and increases in CD4 cell counts at 3-and 6-month follow ups compared with the baseline values.[8]

Reynolds using a multisite RCT, tested if a standard clinic-based patient education with structured and proactive telephone calls delivered over a 16-week period improved treatment adherence better than standard clinic-based patient education. Telephone support participants self-reported higher adherence rates and had lower risk for virologic failure at the final endpoint compared to controls. The finding suggested that telephone delivered interventions can be an effective means to reinforce medication adherence. Because numerous studies demonstrated the effectiveness of telephone-based interventions, the current study used the telephone as a vehicle to deliver MI for 54 antiretroviral adherence improvement interventions in HIV-infected persons living in rural areas. The current study examined the effectiveness of a single session of telephone administered MI to improve medication adherence in rural persons living with HIV/AIDS.[22]

Self-reported data assessing dose adherence and schedule adherence were the primary outcome measures and were assessed through self-administered medication diaries. Participants completed two medication diaries over the course of 5 weeks. A two-week adherence diary reported on adherence prior to the intervention (baseline adherence at week 1 and week 2). A three-week medication diary reported on their medication adherence during the week of the intervention (week 3) and for two weeks following the intervention (post-intervention adherence at week 4 and week 5). Changes in self-reported medication adherence in intervention participants were compared to those reported by participants assigned to a self-monitoring comparison condition. The current study tested the hypothesis that compared to control participants; adherence intervention participants would report greater increases in self-reported rates of medication adherence from baseline to post-intervention.[22]

A randomized controlled trail conducted in the three largest hospitals in China. In this study adherence was measured by self completed questionnaires. Outcome was assessed at day 15 at 1, 2 and 3 month after start of treatment for treatment naïve and at 3 month after study enrollment. A total of 103 treatment naïve and 93 treatment experienced HIV/AIDS patients show that phone call intervention could maintain high self reported adherence among both treatment naïve and treatment experienced patients. After 3 month significant QOL improvement were observed in domain of physical health and levels of independence.[23]

5.2 Strategies to improve ARV medication adherence

5.2.1 Counseling

Counseling forms the main stay of any treatment program. Counseling aims to improve patients' knowledge about the disease and knowledge about the medication and side effects. Counseling helps patient to set goals, to develop positive belief and to increase self efficacy in addition to counseling patient often need other forms of support to able to adhere to treatment.[15]

Motivational interviewing (MI) is a client centered counseling method that helps clients resolve ambivalence toward and build motivation for behavior change. MI counseling has been successful in changing many health behaviors including substance use, fruit and vegetable intake, and physical activity. More recently MI has been used with HIV positive persons to address substance use, medication adherence, and safer sex preventive behaviors. MI promotes both adherence to medication and reduction of risk of HIV transmission.[24]

On study conducted on HIV infected women for 2weeks have higher mean adherence rates: report more frequent mean use of risk reduction behavior: have higher mean CD4 lymphocytes count and lower HIV viral load levels as measured by chart reviews of 3rd, 6th and 9th month. Patient education involves dedicated time with patients to plan for and support medication adherence. The nature and frequency of these interventions vary, but those that appear effective are characterized by an initial educational session including individualized collaborative medication planning with follow-up sessions maintained regularly over the course of treatment.[24]

A prototype for such an intervention derives from a randomized controlled trial (RCT) of 116 individuals initiating their first or second regimen of ART in the Netherlands. The intervention group received an individualized educational counseling session at baseline and at each follow-up visit (0, 4, 24, and 48 weeks) designed to increase knowledge and "self-efficacy" regarding treatment adherence. Specifically, information was provided about HIV and its treatment as well as the relevance of adherence in clinical outcomes and preventing resistance. In addition, a personalized dosing schedule was developed with the patient and plans about how to manage side effects were made. During follow-up visits, strategies for solving any encountered problems were developed. The most common strategies were to design a new drug-dosing schedule, to develop habits that make remembering doses easier, and to provide additional skills to manage mild side effects.[25]

The control group received standard-of-care clinical follow-up. At week 48, 94% in the intervention group vs 69% of those in the control group achieved >95% self-reported adherence; 89% of the intervention group vs 66% of the control had HIV viral loads <400 copies/ml The intervention was found to prevent the decline in adherence commonly seen over time. Both groups started with good adherence, and the intervention helped maintain it, although adherence in the control group progressively worsened.[25]

A randomized controlled trial involving 170 Spanish patients on stable ART found a similar effect. The intervention was a pharmacist-led individualized education and supportive counseling session at baseline with follow-up telephone sessions focusing on adapting medication scheduling to the patient's lifestyle. After 24 weeks, 76% of intervention group vs 52.5% in the control group had >90% self-reported adherence and

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there was a small trend in the intervention group towards improved virologic suppression.[26]

Other randomized controlled trials in Europe and the United States have confirmed that dedicated time with patients to plan for and support medication adherence leads to improved adherence and virologic suppression. The importance of maintaining this support over time is further illustrated by an uncontrolled study that found a significant improvement in adherence over a 4-week study period with an intervention based upon ongoing education and financial rewards for good adherence. However, 4 weeks after the intervention was discontinued, adherence in the intervention group returned to baseline levels.[27]

On the other hand, in a study to assess the impact of 4 weekly educational sessions in 196 HIV-positive patients belonging to minority groups in the United States, at no point during the 24-week follow-up did the intervention and control groups differ in terms of MEMS adherence, viral load, or CD4 count. Therefore, it remains unknown what constitutes an effective educational intervention and for whom it may work.[28]

5.2.2 Directly Observed Therapy (DOT)

DOT has been identified as a possible means of helping patients with difficulties adhering to ART. DOT is an intensive program in which patients take medication under supervision of adherence staff. In TB, DOT is more regimented and provides a tighter monitoring to medication in take in case of ART, it is not practical to observe all doses as most HAART regimen have multiple doses and treatment is lifelong. Therefore, only some doses are observed for a fixed period of time (few months) this is called modified DOT or DAART.[17]

DAART can be done at the health center, in community-based organization or even at patients home. It is used as behavioral intervention that helps patient to develop understanding of the treatment, to develop good treatment taking behavior, to receive support during 1st few weeks of ART when patient have short term side effect and to develop a trusting relationship with provider. Due to evident difficulties with medication adherence, DOT in HIV has been evaluated in a number of recent studies in the developed and developing world.[9]

ARV had been provided in the context of an established DOT program for TB. DOT is feasible and can improve clinical outcomes. However, DOT is expensive, labor intensive, and potentially perceived as intrusive. It remains unclear which populations of patients warrant DOT. It is important to recognize the myriad differences between TB and HIV prior to extrapolating the experience of DOT from one disease to the other. Care should be taken to ensure that DOT programs in HIV care remain optional and voluntary unless an unequivocal public health benefit can be established in the particular population of patients in question.[29]

One study compared 50 incarcerated participants who received their initial ART through DOT with 50 patients initiating ART at an outpatient clinic who monitored their own medication. Those who received DOT had a significantly higher chance at any point in the study of achieving an undetectable viral load. For example, after 48 weeks, 100% of the DOT group had viral loads <400 copies/mL compared with only 68% of the self-monitored patients. [30]

The first randomized controlled trial of community-based DOT followed 112 HIV-positive, actively drug-using individuals for 6 months. Those in the intervention group received all of their medication each day in a blister pack from multidisciplinary personnel. For those on a once-daily regimen, all doses were directly observed. Those on a twice-daily regimen received modified DOT (DAART); 1 dose was observed and the other packet of medication was dispensed to the patient. Those in the control group received standard-of-care follow-up. After 6 months, compared with those in the control group, the patients receiving DOT had significant improvements in 3-day self-reported medication adherence (+32% vs +8%), 6-month median CD4 count (+151 cells/μL vs +20 cells/μL), and 6-month median log reduction of viral load (-2.01 copies/mL vs -0.41 copies/mL).[31]

A prospective study of m-DOT in a methadone clinic provided m-DOT (witnessed morning doses and prepackaged evening doses) for 12 months to 50 HIV-infected drug users (DUs).Their outcomes were compared with those for 2 groups of control patients: 90 matched patients from the same methadone clinic (DU controls), and 146 patients without a history of drug use (non-DU controls). At 6 and 12 months, m-DOT patients (DUs) were significantly more likely to achieve full viral suppression (<50 copies/mL) than were DU controls and were somewhat more likely to achieve full viral suppression than were non-DU controls. Median increases in CD4 counts at 12 months, however, were similar in all groups.[17]

DOT also has been studied in pregnant women thought to be at high risk for nonadherence and consequent mother-to-child transmission. Eight HIV-infected pregnant patients who were hospitalized for DOT during their third trimester were identified by chart review. Their outcomes were compared with those of 32 controls. The main outcome measure was success of therapeutic goals, defined as: no perinatal transmission, suppression of viral load to <1,000 copies/mL, delivery by intended route and at planned delivery site, and receipt of appropriate ART during labor. Despite having significantly greater social barriers to care (no family support, nondisclosure, substance abuse, mental illness, and homelessness), DOT patients achieved a level of success similar to that of control patients (63% vs 69%, respectively). [32]

A RCT conducted on 65 HIV infected opiate dependent individuals for 24week. There is difference between DOT and treatment as actual. After 12month of DOT adherence assessed (86% vs 44%) in DOT and actual treatment respectively. Viral load was decreased by (71%vs 34%) in DOT and actual treatment respectively. However after DOT ended difference in adherence diminished by 1month (55% for DOT vs 48% for actual treatment). After 3month of DOT discontinuation the

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difference completely indistinguishable (49% for DOT vs 50% for actual treatment).[33]

5.2.3 Cognitive–behavioral strategies

Adherence interventions that appear most promising include those with cognitive behavioral (CB) strategies based on self-efficacy theory and those which include the training of pharmacists on adherence strategies. The behavioral interventions emphasize self-efficacy; i.e. belief in one's ability to engage in a behavior as a function of choice, effort and persistence. Self-efficacy is increased through social modeling opportunities, which increases motivation to initiate and maintain new behaviors. Group CB interventions provide a forum for modeling skills such as problem-solving, coping, and assertiveness, while promoting attitude and behavior change through increased self-efficacy.[34]

CB interventions have been used to enhance patient responses to stressors and encourage active coping strategies to reduce the deleterious affective and behavioral sequelae of HIV infection. Patients obtain knowledge, adopt group norms of behavior and share concerns with peers, develop illness-management skills, improve coping and quality of life, and reduce anxiety and depression while increasing medication adherences. [35]

On randomized trial conducted by Peltzer and his colleagues a total of 152 patients enrolled in the study 76 in the experimental and 76 in the comparison group. Analysis of variance between intervention conditions on the adherence information knowledge test scores at pre- and post intervention showed a significant increase in the intervention compared to the control group at follow-up. Adherence motivation and skills did not significantly change among the intervention conditions over time. Analyses found a significant improvement of ART adherence and CD4 count and a significant reduction of depression scores over time in both intervention and control conditions; however, no significant intervention effect between intervention and control conditions was found. With higher ART adherence CD4 counts increased and depression symptom scores decreased. Again, no significant group time interaction effect was observed for the total group for either measure [34]

Two arm RCT conducted by Safren and his colleagues on 300 patients comparing CBT to enhance treatment as actually only. At the acute outcome assessment (3 month) those who receive CBT evidenced significantly greater improvement in medication adherence and depression relative to the comparison group.[36]

6. CONCLUSIONS

Adherence to ART is closely tied to virologic, immunologic, and clinical outcomes. Small increases in adherence can result in significant improvements in these outcomes. To help patients benefit fully from ART, health care workers need to take time to ask about and support medication adherence. Many methods are used to assess adherence; in clinical practice, patient self-report is the most simple and economical.

There are many ways available for health care workers to support and improve medication adherence. Alterable factors known to affect adherence, such as patient factors, regimen complexity, medication side effects, and the therapeutic relationship between patient and provider, can be addressed prior to starting therapy and in an ongoing way throughout treatment. During therapy, the detection of nonadherence is itself a valuable accomplishment.

Improving adherence requires collaborating with the patient in an effort to understand and ameliorate individual impediments to adherence, generally by establishing dedicated time with every patient to educate, plan for adherence, and maintain support and collaboration throughout the course of treatment. In this way, adherence can be regularly assessed, problems can be addressed, side effects can be dealt with, medications can be simplified or changed if necessary, and adherence devices can be used where appropriate.

7. FUTURE PERSPECTIVE

Finally, future research and practice should consider intervention approaches that address the live experience of individuals in HIV care, which includes adherence challenges for those on ART and other life priorities that influence treatment adherence. Collaboration with patients, in recognition of their often trying life circumstances, multidisciplinary involvement with the best prospects is crucial for optimal health outcomes.

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